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Conformational analysis of gossypol and its derivatives by molecular mechanics

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Abstract

Conformations and inversion pathways leading to racemization of all the tautomers of gossypol, gossypolone, anhydrogossypol, and a diethylamine Schiff's base of gossypol were investigated with MM3(2000). All forms have hindered rotation because of clashes between the methyl carbon atom and oxygen-containing moieties *ortho* to the bond linking the two naphthalene rings. Inversion energies generally agree with available experimental data. Gossypol preferentially inverts in its dihemiacetal tautomeric form through the *cis* pathway (where similar groups clash). Gossypolone inverts more easily than gossypol, and preferentially through the *trans* pathway (where dissimilar groups clash) when one of its outer rings has an enol-keto group and the other has an aldehyde group. Anhydrogossypol racemizes through the *cis* pathway. The bridge bond and the *ortho* exo-cyclic bonds in all the structures bend from planarity, and the inner naphthalene rings pucker to accommodate the inversion. For gossypol, the transition is achieved through greater bending of the exo-cyclic bonds (up to 12°) and less distortion of the inner benzyl rings ($q \leq 0.34$ Å), (up to 12.7°) . For gossypolone the transition occurs with greater distortion of the inner benzyl rings ($q \leq 0.63$ Å) and less out-of-plane bending (up to 8.4°). By isolating individual clashes, their contribution to the overall barrier can be analyzed, as shown for the dialdehyde tautomer of gossypol.

Keywords: Anhydrogossypol; Binaphthalene; Conformations; Gossypol; Gossypolone; MM3; Molecular mechanics

1. Introduction

Gossypol [2,2′-bis(8-formyl-1,6,7-trihydroxy-5-isopropyl-3-methyl)naphthalene] (Fig. 1), a yellow pigment in cottonseed, can be toxic to nonruminant animals when cottonseed serves as feed [1]. Because of steric hindrance around the central bond connecting the two substituted naphthalene rings, two stable enantiomeric gossypol forms exist. This steric hindrance is caused by the methyl, hydroxyl, and/or hemiacetal groups *ortho* to the central bond clashing during rotation about the binaphthalene bridge. The two forms show considerable differences in toxicity and biological activity [2,3], which leads to interest in understanding their potential to racemize. Although gossypol is relatively resistant to racemization, some Schiff's bases of gossypol invert [4,5].

The absolute configurations of the gossypol (+) and (−) enantiomers have been determined by vibrational and electronic circular dichroism [6,7], with the (−)-enantiomer being the M-form. Numerous gossypol crystal structures have been obtained [8] and a recent structure of (−)-gossypol confirms the M-form assignment [9].

Experiments to ascertain the energy barrier for preventing gossypol racemization are difficult, in part because gossypol dehydrates to anhydrogossypol at elevated temperatures [10]. To bypass experimental problems, Jaroszewski et al. investigated the gossypol racemization energy barrier by computation with the molecular mechanics program MM2(87) [10]. They analyzed the aldehyde tautomeric form of gossypol (gossypol 1, Fig. 1) and a number of simpler model compounds with aldehyde and hemiacetal *ortho* substituents, along with a model compound of anhydrogossypol. The study, however, did not consider other potentially important gossypol derivatives. For instance, besides anhydrogossypol, which

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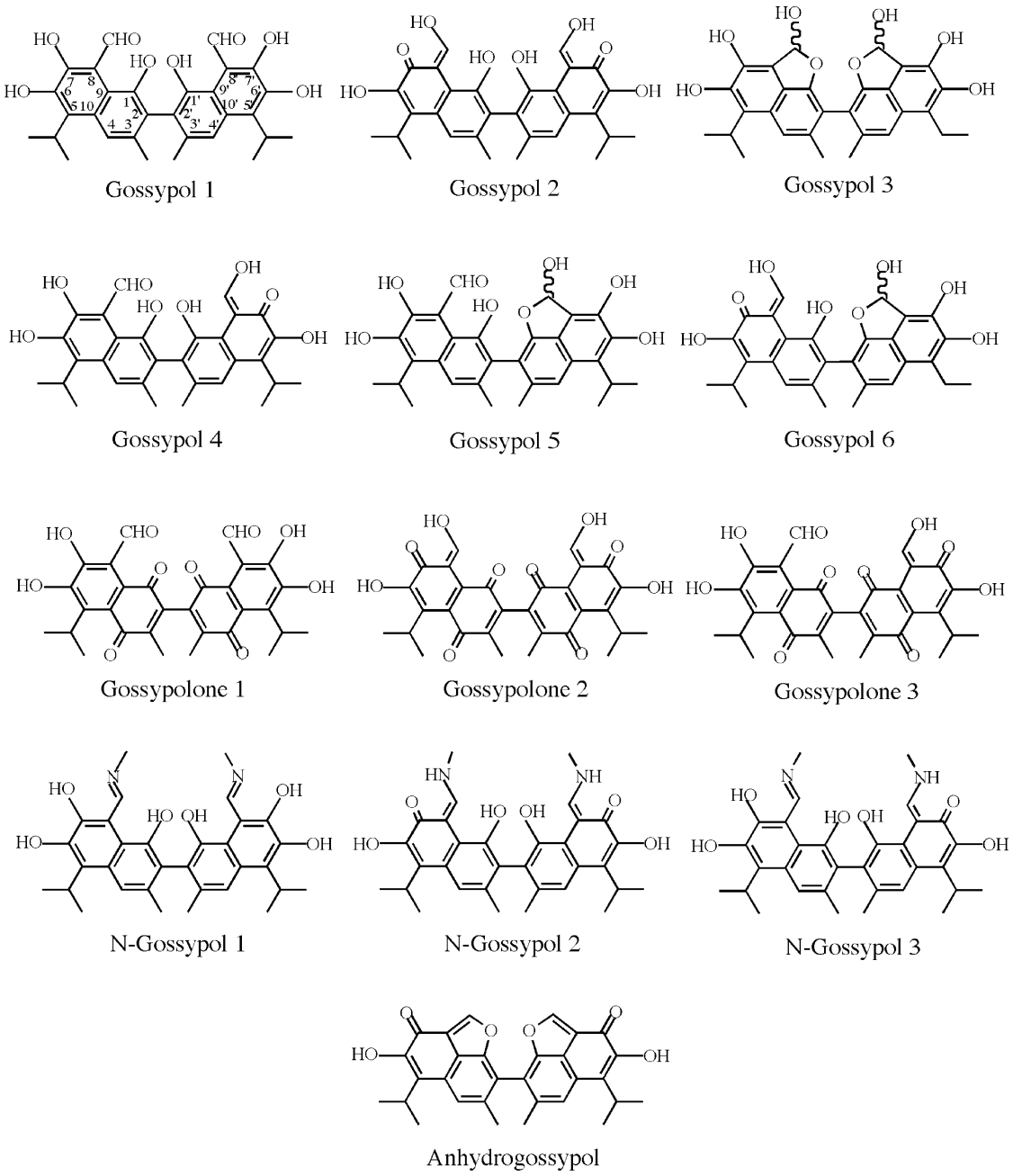

Fig. 1. Tautomeric structures of gossypol, gossypolone, N-gossypol, and anhydrogossypol.

racemizes somewhat easier than gossypol [10], gossypolone is a gossypol oxidation product [11] that readily racemizes at room temperature [12]. In addition, tautomers arise from rearrangements around the aldehyde groups in gossypol and gossypolone and the amine group in Schiff's base amine derivatives of gossypol (N-gossypol). Three rearrangements exist for gossypol and two exist for gossypolone and N-gossypol, resulting in six, three, and three structures, respectively (Fig. 1). In addition, another set of structures is possible for the hemiacetal tautomers of gossypol, as they have chiral hydroxyl groups.

Molecular mechanics was previously used to study not only gossypol and anhydrogossypol [10], but also binaphthalene and related derivatives [13,14]. We have used the molecular mechanics program MM3 to investigate other ring-bridged compounds (*i.e.* disaccharides) [15,16] and five- and six-atom ring puckering (*i.e.* furanose and pyranose rings) [17,18].

The overall goal of this project was to study the inversion pathways of gossypol and its derivatives to determine the nature of each pathway and its relationship to current experimental data. We have thoroughly investigated ten

tautomers (Fig. 1), including six of gossypol, three of gossypolone, and the one of anhydrogossypol, with MM3, version 2000 [19–21]. Three N-gossypol tautomers were also studied but in less detail.

2. Computational methods

Molecular simulations were conducted on a Dell PC with an 800-MHz Pentium III processor. MM3(2000) was obtained from Professor N. L. Allinger of the University of Georgia. All structures were created with MEDIT, an interactive molecular editing and display program included in the MM3 package, and were studied with the default parameters. The isopropyl groups were oriented with the methyl groups directed outward and away from the center of the molecule, as this has been reported to be the lowest-energy form from a recent DFT calculation [7] and as it is generally found in gossypol crystal forms [8]. Minimal energy structures were initially produced for all 13 structures by the block-diagonal followed by full matrix minimization method with the default convergence criteria. The corresponding enantiomer for each structure was generated by changing the sign of one of the coordinate axes of each atom. A final minimization was conducted to ensure that both enantiomers were in a minimal-energy state.

Each structure was forced to invert by driving the central dihedral angle (defined by C3–C2–C2′–C1′ throughout) in 1.5° increments until reaching the opposite enantiomer. Two potential inversion pathways exist that require overcoming either a *cis* interaction (a clashe of two methyl groups as well as a clash of two oxygen substituents) or a *trans* interaction (two clashes of methyl groups and oxygen substituents). Generally, energies increase as the rings are forced toward planarity until a break point is reached that relieves the strain of the clashing atoms. Energy barriers were approximated from the difference in the highest energy found before the break point and the minimum energy found near 90 or −90°.

For each inversion trajectory, out-of-plane bending angles (α) were calculated for the *ortho* substituents and the appropriate C2 (or C2′) carbon atoms. These were determined from the projected plane formed by the three naphthyl ring atoms and the bond between the atom in question with the central atom (Fig. 2).

In addition, the extent of puckering of each inner naphthalene ring was monitored following Cremer-Pople formalism [22]. In this method, three terms, q, θ, and ϕ, are used to describe six-atom ring puckering. The average deviation of the atoms in the inner naphthalene ring from a least-squares fit plane is represented by q. The positioning of the puckering about the ring is described by θ and ϕ. The numbering of the ring atoms for this analysis was C1–C2–C3–C4–C10–C9 or C1′–C2′–C3′–C4′–C10′–C9′.

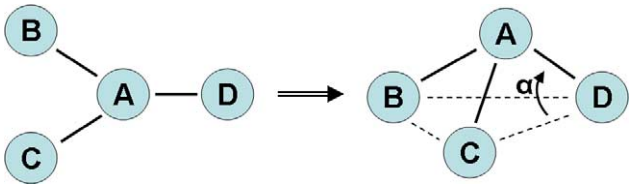

Fig. 2. Definition of out-of-plane angle α for atom D.

3. Results and discussion

3.1. Minimal structures

Both enantiomers of all 13 structures were successfully minimized, with corresponding characteristics displayed in Table 1. Only characteristics of the (+)-enantiomer are included, as all corresponding (+) and (−) enantiomers have identical steric energies and dihedral angles, which is expected from their symmetrical natures. The naphthalene rings in each minimal structure are approximately perpendicular to each other [−80° to −90° and +80° to +90° for the (+) and (−) enantiomers, respectively], differing somewhat with the approximately −70 and +70° values found by MM2 for gossypol 1 [10]. In comparison, the angle between the best-fit naphthalene planes of gossypol crystal structures covers from about 70 to 110° [8], essentially spanning the range of modeled values. The length of the central dihedral bond varied among minimal structures (Table 1). Out-of-plane angles for the major *ortho* groups were all <1°.

Orientations of the hydroxyl and isopropyl groups are consistent with both crystallography [8] and DFT calculations [7]. As was found by the latter, MM3 optimization of the isopropyl methyl groups directed inward toward the center of the molecule had slightly higher energies than

Table 1
Characteristics of the (+)-enantiomer of minimal energy structures

Structure	E (kcal/mol)	Dihedral angle (°)	d (Å)	q (Å)	
				C1–C2–C3–C4–C10–C9	C1′–C2′–C3′–C4′–C10′–C9′
Gossypol					
1	33.1	85.8	1.520	0.100	0.100
2	32.7	88.5	1.521	0.062	0.062
3	22.0	82.0	1.506	0.022	0.019
4	32.6	85.2	1.520	0.057	0.102
5	27.7	80.8	1.510	0.103	0.026
6	27.5	81.1	1.510	0.056	0.025
Gossypolone					
1	42.9	83.8	1.507	0.371	0.372
2	39.5	82.9	1.506	0.361	0.373
3	43.7	88.8	1.508	0.373	0.414
Anhydrogossypol					
	54.5	82.6	1.506	0.004	0.004

Steric energy (E), dihedral angle (C3–C2–C2′–C1′), length (d) of central dihedral bond, and puckering length (q) for inner naphthalene rings.

when the methyl groups pointed outward away from the center of the molecule. The lower-energy outward orientation was used throughout this study. The aldehyde groups of gossypols 1, 4, and 5 and gossypolones 1 and 3 are rotated away from the extended naphthalene ring plane by ~40°, which is inconsistent with diffraction data that place the carbonyl oxygen within the extended naphthalene plane [8]. This difference was also evident in the previous MM2 study of gossypol [10] but not in the DFT calculations [7], and this may indicate the need for more accurate parameters to model the benzyl aldehyde torsional angles or some modification to the hydrogen bonding functionality.

3.2. Inversion pathways

Starting from the minimal structures, each central dihedral angle was driven in each direction to the opposite enantiomer. Rotation results in gradually increasing energies as the molecules deviate from their preferred conformations, with abrupt energy breaks occurring as each clash was overcome. Fig. 3A is a suitable example, where gossypol 1 proceeds through both inversion pathways from both directions. *Trans* and *cis* clashes occur around 0 and 180°, respectively. Inversion through the *cis* clash yields two breaks: first passage of hydroxyl groups and then passage of methyl groups.

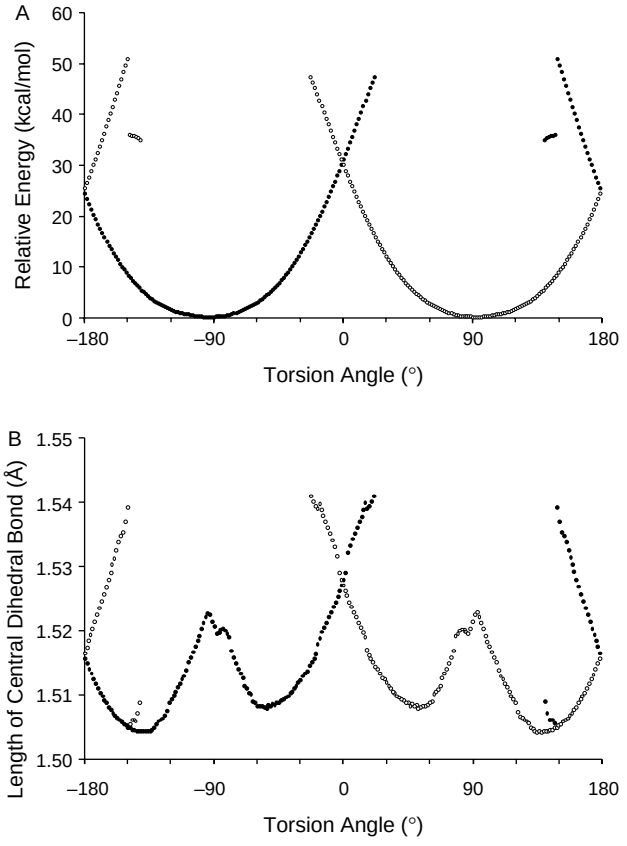

Fig. 3. Relative energies (A) and C2–C2′ bond lengths (B) for the inversion pathways of gossypol 1 for (+) and (−) enantiomers (closed and open circles, respectively). The dihedral angle is defined by atoms C3–C2–C2′–C1′.

Fig. 3B shows the C2–C2′ bond length of gossypol 1 at different dihedral angles. Its behavior is much more complex than the energies shown in Fig. 3A, as bond length is affected by opposing forces. As the rings rotate away from their optimal conformations, bond length initially shortens as the conjugation increases through the binaphthalene bond and the rings become more planar. With increasing rotation, steric influences overcome the conjugation effects and the bond lengthens. Bond length reaches its maximal value near the clashes. The C2–C2′ bond length in gossypol 1 is increased by about 0.02 Å over its value at the low-energy optimum. The observed central dihedral bond lengths of the minimal structures (Table 1) are very similar, since the naphthalene rings are approximately perpendicular, resulting in loss of conjugation across the bond.

Energy barriers were determined from the inversion pathways. Table 2 contains data for inversion from the (+) to the (−) enantiomers for all 13 structures. Data for the reverse inversion pathways are omitted since they are consistently identical. The first and second break angles in the table occur when clashing substituents pass each other, followed by immediate relaxation of the structure. Breaks occur either sequentially, as in many *cis* clashes, where hydroxyl groups or ring oxygen atoms pass each other

Table 2
Characteristics of the inversion pathways for thirteen gossypol forms

Structure	*Cis* clash (180°)			*Trans* clash (0°)	
	Max ΔE (kcal/mol)	Relative break angle (°)		Max ΔE (kcal/mol)	Relative break angle (°)
		1	2		1
Gossypol					
1	50.8	31	40	47.1	22
2	56.9	33	–	50.2	28
3	31.7	16	36	42.2	37
4	39.9	7	38	50.3	40
5	40.6	21	35	49.5	35
6	49.6	29	33	49.5	35
Gossypolone					
1	19.4	14	–	20.3	−5
2	22.2	14	–	13.8	15
3	21.9	11	–	14.1	−2
N-Gossypol					
1	50.8	34	40	49.4	25
2	56.7	32	–	51.0	30
3	49.3	30	–	51.5	29
Anhydrogossypol					
	31.2	32	–	37.9	34

Breaks occur when *ortho* substituent groups pass each other and the structure abruptly relaxes. If two breaks occur, hydroxyl groups or ring oxygen atoms pass first, followed by the two methyl groups. Max ΔE: maximal relative energy needed to cross energy barrier; relative break angle: dihedral angle deviation from either 0 or 180° where the specified break occurs.

followed by methyl groups, or concurrently, as in all *trans* clashes.

All gossypol tautomers have high energy barriers. Inversion of gossypol 3 through the *cis* clash requires the least energy (31.7 kcal/mol), since its ring oxygen atoms are pulled away from the atoms of the opposite ring more than the hydroxyl groups of gossypols 1 and 2. This value can be compared with the roughly 35 kcal/mol calculated by MM2 for a model compound of gossypol 3 [10]. Gossypol 1 has energy barriers of 50.8 kcal/mol for inversion through the *cis* clash and 47.1 kcal/mol for inversion through the *trans* clash, compared to >50 kcal/mol for varieties of its model compounds, again calculated by MM2 [10]. Hybrid tautomers (gossypols 4–6) often have energy barriers between those of their respective symmetrical tautomers. Even the gossypol 3 energy barrier would be impassable at room temperature, as is observed experimentally in 3:1 dioxane/water [10].

Gossypolone has energy barriers ranging from 13.8 to 22.2 kcal/mol. These reduced energies are due in part to the shorter bond length of the carbonyl oxygen atoms compared with the hydroxyl and ethereal oxygen atoms in the gossypol structures, but it is also due in part to a lower energy of distortion of the inner quinoid rings compared to the phenolic rings of gossypol (discussed below). The lower gossypolone energy barriers, which include inversion through the *trans* clashes of gossypolone 2 and 3, are consistent with recent data suggesting gossypolone readily racemizing at room temperature [12].

Anhydrogossypol requires at least 31.2 kcal/mol to racemize through the *cis* inversion pathway, which should occur at temperatures similar to those of gossypol 3, as inferred from experimental data [10].

When compounds like gossypol exist as multiple tautomers, they should preferentially racemize by their lowest-energy pathways, those being gossypol 3 through a *cis* clash and gossypolones 2 and 3 through *trans* clashes. If all tautomers of a species exist in the same solution at or near equilibrium, racemization should occur even if the principal tautomer in the solution has a high-energy pathway. However, the rates of racemization will be affected by the tautomer distribution. This does not appear to be significant with gossypol, as dehydration to anhydrogossypol will tend to occur before direct racemization [10]. Still, experiments at elevated pressure in solvents with water may allow for such observations.

Limited modeling was conducted on diamine Schiff bases of gossypol to highlight a difficulty in understanding and modeling gossypol racemization. Some gossypol amines invert at room temperature in solution [4,5]. The effect appears to occur more readily when the compounds are exposed to sunlight, and solvent may also influence the reaction, although the latter effect has not been studied explicitly. Because the N-gossypol compounds cannot tautomerize into hemiacetal forms, they cannot take the shape favored by gossypol (e.g. gossypol 3) for racemization. This suggests that these compounds should be less able to invert, which contradicts experimental observations. With MM3, the imine and enamine forms of N-gossypol have energy barriers similar to those of gossypols 1, 2, and 4, all with rotation barriers between 49 and 57 kcal/mol. This result indicates that molecular mechanics is not able to encompass all of the interactions occurring during gossypol inversion, such as electronic and free radical interactions.

3.3. Ring planarity and substituent bond bending

Extents of puckering (q) for the inner naphthalene rings, out-of-plane angles for the *ortho* substituents and the central dihedral bond, and central dihedral bond lengths are shown in Table 3. The maximal values typically occurred within approximately 10° of the angle at which the maximal energy occurred. Planarities of the maximal (Table 3) and minimal energy structures (Table 1) are similar for all six gossypol tautomers, as they are for the three gossypolone tautomers. The six gossypol tautomers have q values generally between 0.2 and 0.3 Å, with the inner rings of gossypol 1 undergoing a *cis* clash being the most deformed and those of gossypol 3 being the least, which agrees with its having the smallest energy barrier. Gossypolone tautomers have average q values between 0.5 and 0.6 Å (Table 3), the higher values resulting from the increase of ring flexibility caused by its less delocalized ring structure. This may be compared to $q=0.213$ Å for the crystal structure of gossypolone 1 [23], suggesting a significant difficulty in modeling this structure. The inner rings of anhydrogossypol deform the least, with q values between 0.15 and 0.2 Å, expected given the added rigidity caused by the adjacent oxygen-containing bridging rings. Gossypol 3, whose structure is very similar to that of anhydrogossypol, has similar q values that are subsequently the smallest values associated with any of the gossypol tautomers. The most significant stretching of the central dihedral bond occurred in gossypols 2, 5, and 6 to compensate for their high energy barriers among all tautomers of gossypol, gossypolone, and anhydrogossypol.

Out-of plane angles are highest for gossypol, slightly lower for anhydrogossypol, and substantially lower for gossypolone, opposite to the results with q. These angles, as well as the dihedral angle deviations found in Table 2, show that the *ortho* substituents and the central C2–C2′ bond bend during inversion to facilitate passage of the sterically clashing groups. The central bond bends more than either substituent group *ortho* to it for all 10 structures, indicating that the molecule folds around the central bond during inversion more than the *ortho* substituent groups are forced to bend. Significant central-bond bending was also seen in MM2 studies of modified binaphthalenes [13,14]. The different responses shown by out-of-plane angles and values of q for different gossypol species indicate that strain is

Table 3
Maximal out-of-plane angles, values of q, and increase in length of central dihedral bond from the minimal energy structure (Δd) for both inner naphthalene rings during inversion through the *cis* and *trans* clashes

Structure	C1–C2–C3–C4–C10–C9			q (Å)	Δd (Å)	C1′–C2′–C3′–C4′–C10′–C9′			q (Å)
	Out-of-plane angle (°)					Out-of-plane angle (°)			
	CB	CH_3	OH			CB	CH_3	OH	
Cis clash (180°)									
Gossypol									
1	9.82	7.27	4.30	0.336	0.019	8.38	5.50	8.87	0.317
2	10.79	10.25	4.37	0.258	0.032	8.70	4.36	7.45	0.205
3	8.52	7.62	2.77	0.207	0.019	8.43	5.48	6.44	0.216
4	9.47	6.87	2.02	0.245	0.023	10.29	6.04	6.49	0.303
5	9.32	7.59	4.32	0.325	0.018	8.65	5.08	7.58	0.236
6	10.34	8.05	4.37	0.314	0.028	9.68	6.04	8.55	0.263
Gossypolone									
1	7.64	4.73	2.18	0.567	0.003	4.48	0.89	1.87	0.562
2	6.58	5.38	2.09	0.555	0.004	5.12	0.99	2.28	0.541
3	7.38	4.65	2.34	0.540	0.001	6.78	1.55	2.61	0.634
Anhydrogossypol									
	7.52	7.96	2.39	0.168	0.011	7.77	4.84	6.11	0.199
Trans clash (180°)									
Gossypol									
1	11.96	7.96	2.04	0.187	0.021	11.75	4.63	4.69	0.265
2	11.49	8.32	1.99	0.118	0.021	11.79	5.34	4.26	0.295
3	12.04	6.34	2.86	0.081	0.020	10.56	6.08	6.46	0.283
4	12.70	6.94	3.99	0.267	0.022	10.73	4.12	6.85	0.303
5	12.06	7.37	1.55	0.192	0.032	11.41	6.14	7.37	0.315
6	11.78	7.74	1.52	0.134	0.029	11.30	6.34	7.18	0.313
Gossypolone									
1	8.41	5.33	1.67	0.566	0.004	8.00	1.52	2.07	0.552
2	6.67	2.51	2.09	0.525	0.005	4.53	1.35	1.89	0.563
3	7.31	3.59	1.99	0.554	0.001	4.23	1.23	2.66	0.582
Anhydrogossypol									
	11.67	6.21	3.13	0.084	0.016	10.04	5.82	5.40	0.236

Angles specified for central dihedral bond (CB) and for methyl (CH_3) and oxygen (O) substituents *ortho* to the bond.

distributed to varying degrees among ring distortion, bond stretching, and bond bending effects.

For the nonsymmetrical molecules (e.g. gossypols 4, 5, and 6), the individual values should not be identical. However, identical values are not found even for symmetrical molecules (Table 3). For these molecules, differences in q and out-of-plane bending angles highlight the difficulties of trying to model transition states by driving a single dihedral angle and forcing the rest of the molecule to respond to the induced stress. As has been noted before [13,14], molecular models of transition-state pathways are not likely to coincide with "true" transition-state mechanisms. In part this arises because of the limitations of the underlying model, but it also arises because of the choice of a specific trajectory to follow through the transition state that may not represent the most probable pathway. However, even with a "fixed" trajectory, the geometrical changes that occur along the pathway should provide some insight into the inversion mechanism.

In this study, geometries change gradually, as indicated by slowly changing values of q until a break occurs. If two breaks occur, as in the *cis* inversion of gossypol 1, then the geometry of one ring changes abruptly at each break as the stress response is redistributed among the remaining clash elements. If only one break occurs, as in a *trans* inversion, then both rings substantially change. In gossypolone, no significant puckering change occurs for many of the breaks.

3.4. Steric contributions of each clash

To reduce the complexity of each inversion pathway, we dissected the contributing factors by studying single clashes rather than the two that contribute to the overall steric hindrance. One clash can be ameliorated by replacing the groups participating in it with hydrogen atoms. Three reduced structures based upon gossypol 1 were generated (Fig. 4) by removing both methyl groups (no CH_3), both hydroxyl groups (no OH) or a hydroxyl group and a methyl group (no OH/CH_3). The no CH_3, no OH, and normal gossypol 1 structures were driven through the *cis* clash, while the no OH/CH_3 and normal gossypol 1 structures were

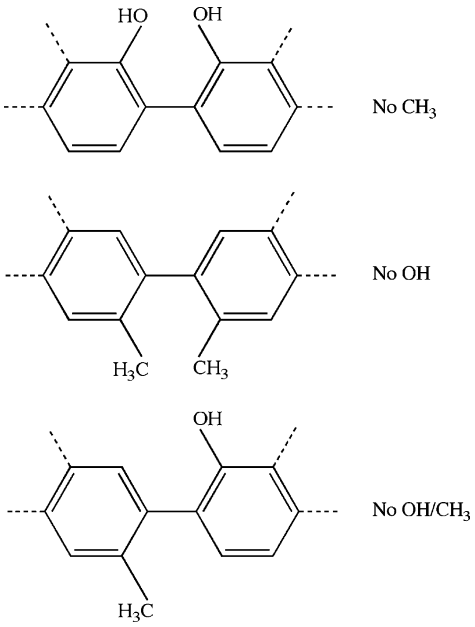

Fig. 4. Reduced structures of gossypol 1 generated by removing methyl groups (no CH_3), hydroxyl groups (no OH), or one hydroxyl and one methyl group (no OH/CH_3).

driven through the *trans* clash, giving the relative steric energies plotted in Fig. 5.

The additive nature of the individual clashes is immediately apparent, although there are some coupling

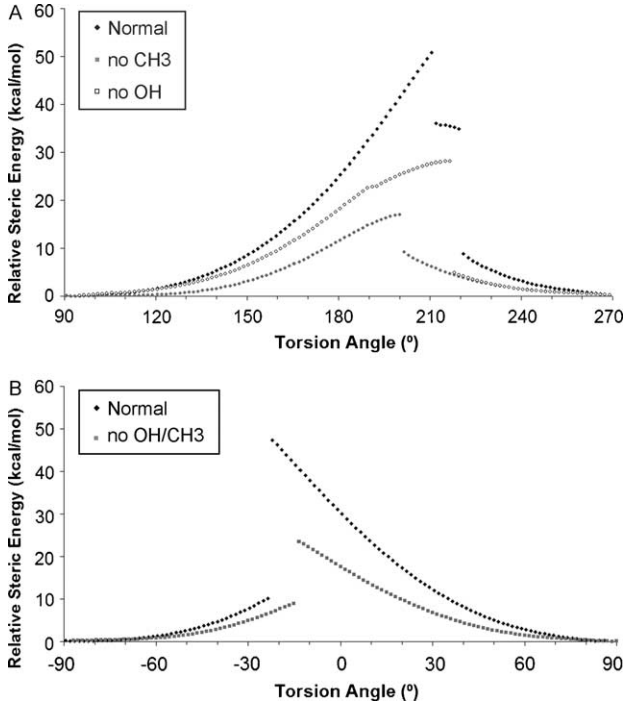

Fig. 5. Relative energies (A) for the normal (closed diamonds), no CH_3 (gray diamonds), and no OH (open diamonds) forms of gossypol 1 driven through a *cis* clash and (B) relative energies for the normal (closed diamonds) and no OH/CH_3 (grey squares) forms of gossypol 1 driven through a *trans* clash.

effects. The two separate clashes of the *cis* inversion pathway well represent the nature of the normal structure (Fig. 5A), where paired hydroxyl groups break before paired methyl groups. The first break of normal gossypol 1 occurs after the individual hydroxyl-hydroxyl (no CH_3) break, while its second break occurs after the methyl–methyl (no OH) break. Additionally, the average energy barrier of the two reduced clashes is 44.3% of that for the normal clash, compared to 50% when no coupling occurs. This behavior may be attributed to the ability of the reduced structures to contort more easily and bypass the clash. The *trans* clash more typifies an additive nature, where the break of the no OH/CH_3 form occurs 9° before that of the normal form, while its energy barrier is 49.7% of the latter (Fig. 5B).

Decomposing gossypol into reduced structures featuring individual clashes was very insightful into understanding the energy barriers of the original structure. It revealed the additive nature of the individual clashes, although the same result is not predicted for asymmetric molecules. Such a process should be applicable in decomposing the results contained in Table 2, including the hybrid tautomers.

4. Conclusions

The absolute conformations and racemizations of gossypol, gossypolone, and anhydrogossypol were thoroughly investigated with MM3(2000). The results detail the nature of the inversion pathways necessary to racemize each structure through similar mechanisms. Transitions of all enantiomers from either (+) to (−) or (−) to (+) are identical when undergoing the same inversion pathway, thereby confirming their identical nature. When undergoing an inversion, each structure primarily folds along the central bond along with bending of the groups *ortho* to it to overcome the steric clash normally preventing racemization. The nature of the clashes results in varying energy barriers for each structure. Gossypol seems to racemize by preferential inversion of the dihemiacetal tautomer through a *cis* pathway. The transition energy of this inversion is comparable to the transition energy for anhydrogossypol, which inverts at elevated temperatures [10]. Gossypolone has a lower transition energy, confirming the observation that it is not possible to isolate gossypolone enantiomers at room temperature.

Gossypol and its derivatives are complex molecules with unique interactions that can not be completely defined with molecular mechanics. The use of computational simulations allows predictions similar to experimentation in minimal structure and energy barriers, although the aldehyde position in most structures and the observed racemization of N-gossypol demonstrate that more work is needed to further understand this molecule.

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